

Systolic time intervals: a review of the method in the non-invasive investigation of cardiac function in health, disease and clinical pharmacology

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Summary

Measurement of systolic time intervals is a valuable, non-invasive procedure to assess left ventricular performance, particularly when influenced by drugs. In this review, we discuss various factors affecting systolic time intervals, the therapeutic implications of the technique and its place among other non-invasive tests of cardiac function.

KEY WORDS: non-invasive techniques, systolic time intervals, echocardiography, clinical pharmacology.

Introduction

Despite the early introduction of simultaneous recording of the heart sounds, the central arterial pulse tracing and the electrocardiogram (ECG) to define the intervals in the cardiac cycle, their clinical application as an investigative tool received little attention until the early 1960's (Weissler, Peeler and Roehll, 1961). This delay can be attributed to the fact that the physiological implications of the systolic time interval (STI) could not be validated until comparisons with direct measures of cardiac function such as cardiac catheterization and ventriculography became clinically available, and thus the importance of these measurements was appreciated (Weissler, 1977). The determination of STI offers a convenient, non-invasive method to study changes in left ventricular performance (Weissler, Harris and Schoenfeld, 1969) and the effects of therapeutic interventions or diseases on myocardial performance.

Definitions and measurement of systolic time intervals (STI)

The STI (Weissler *et al.*, 1961; 1969; Weissler, 1977) represent the duration of total electro-mechanical systole with its two major components, the pre-ejection and the ejection phases (Fig. 1). The total

electro-mechanical systole (QS2) is the interval that spans the entire period of systole from the onset of the QRS complex on the ECG to the closure of the aortic valve as reflected by the first high frequency vibrations of the aortic component of the second heart sound. The left ventricular ejection time (LVET) is the phase of systole during which blood is ejected into the arterial system, and is measured from the beginning of the upstroke to the trough of the incisural notch on the external carotid arterial pulse tracing. The pre-ejection period (PEP) is the interval from the onset of ventricular depolarization to the beginning of the left ventricular ejection. It is derived by subtracting the LVET from the QS2. The calculation of PEP in this way discounts the time of delay due to transmission of the arterial pulse wave from the proximal aorta to the point of its detection over the external carotid artery (usually about 20 msec). Further attempts to subdivide the PEP into electro-mechanical delay and isovolumic contraction time have proved unsatisfactory. However, in patients with abnormalities of intra-ventricular conduction, determination of the electro-mechanical delay may be of value in the analysis of the duration of the PEP (Weissler, 1977). A simple informative way of presenting the STI can be provided by the use of PEP/LVET ratio (Weissler, 1977).

The STI are measured from simultaneous recording of an electrocardiogram, phonocardiogram and external carotid arterial pulse tracing using a multi-channel photographic recording system. High quality equipment is essential. An ECG lead most clearly demonstrating the onset of ventricular depolarization wave (Q-wave) departing acutely from a flat baseline is required (usually lead II or a precordial lead). The phonocardiogram is recorded from the upper part of the precordium in a position optimal for recording the initial high frequency vibrations of the second heart sound (usually second left intercostal space).

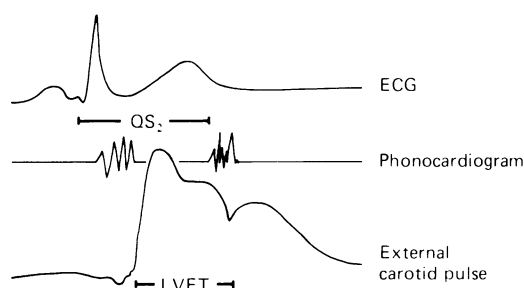


FIG. 1. Simultaneous recording of ECG, phonocardiogram and external carotid pulse tracings showing systolic time intervals. QS_2 = total electromechanical systole; LVET = left ventricular ejection time; $PEP = QS_2 - LVET$.

The microphone used should be in a range of frequency of 100–500 Hz. The external carotid arterial pulse tracing is recorded with a high fidelity strain-gauge transducer that permits a flat frequency response between 0.1 and 30 Hz and at least a 2.0 sec time constant. The transducer is placed firmly over the artery just below the carotid sinus. The arterial pulse tracing must show clearly the upstroke, which is the first thinning of the pulse line above the initial upward displacement of the isovolumic contraction, and a sharp single incisura. Before obtaining a permanent recording, it is advisable to scan an oscilloscopic display of the recordings to ascertain that each of the events from which the calculations are made is sharply inscribed. Ten successive beats are usually registered so as to allow for the effect of respiration (Lewis *et al.*, 1977).

To obtain the best information from this technique, efforts are required to standardize its various technical procedures including those of recording and of measurement. It should be performed at the same time of the day after 5 min rest (Lewis, 1975). Repeated recordings of the STI are preferably done on the same carotid artery for each subject, although no statistically significant difference was found between recordings done on both sides (Van De Werf *et al.*, 1975). For accurate measurement of the STI, a paper speed of 100 mm/sec is required (Weissler *et al.*, 1969). This speed showed the smallest numerical differences in the measurement of STI when compared to other speeds (Spodick, Ball and Pigott, 1978). Calculation of the STI is considered as the mean of the 10 successive intervals. This has to be analysed carefully and without knowing the treatment taken, as changes of 10–30 msec may be the sole finding (Lewis *et al.*, 1976; Kelman, Sumner and Whiting, 1981a). The measurements can either be done manually or with the aid of a programmed computerized digitizer which is quicker (Weerasuriya, 1982). Heart rate is calculated from the R-R interval of the 10 heart beats.

Effect of heart rate on STI and derivation of the regression equations

It has long been appreciated that the systolic phases of the cardiac cycle vary inversely with heart rate (Lewis *et al.*, 1977). Thus, for deviations of STI to be properly interpreted, corrections must be made for variations related to differences in heart rates (Lewis *et al.*, 1977). Regression equations relating each of the STI to the heart rate have been derived for clinical use in different age groups. These equations were used to derive the STI indices. Each in fact, represents the measured interval extrapolated to zero heart rate, thus eliminating heart rate as a significant variable affecting the intervals (Weissler, Lewis and Leighton, 1972). The index is calculated as the sum of the measured interval plus the product of heart rate multiplied by slope of the regression equation. When compared to the normal index of the population, the calculated value gives a quantitative measure of the degree of deviation from normal and offers a convenient expression to study serial changes during drug therapy. Unfortunately, there is no universal agreement about the currently available regression equations (Burgess, Wadsworth and Warrington, 1979) and the best way by which they should be derived. The most widely applied regression equations in practice are those derived by Weissler, Harris and Schoenfeld (1968) from STI recorded in normal subjects with a wide range of resting heart rate. Recently, it has been suggested (Johnson *et al.*, 1981) that they considerably over-correct for heart rate changes and consequently will correct for total effects of altered adrenergic stimulation rather than other factors affecting myocardial contractility. These slopes were similar to those obtained after infusion of isoprenaline (Johnson *et al.*, 1981). In addition, nearly all authors agree that PEP is virtually independent of heart rate (Spodick, 1977; Burgess *et al.*, 1979). Many investigators have used either atrial pacing (Johnson *et al.*, 1981) or incremental doses of atropine intravenously (Burgess *et al.*, 1979) to produce a range of heart rates and derive the regression equations. Kelman and associates (1981a, b) believe that each subject must have his own equations when the inotropic effect of drugs is being assessed by STI.

Each age group has its own regression equations derived from studying normal healthy subjects of both sexes resting supine (Table 1).

Physiological variations of systolic time intervals

Effect of age and sex

Comparison of children, adolescents and adults shows a distinct tendency towards lengthening of all the STI with increasing age, independent of changes in heart rate (Wanderman *et al.*, 1981). Compared

TABLE 1. Various regression equations

Children one month-13 years (Cantor <i>et al.</i> , 1978):	
Male QS2I = $QS2 + 1.6 \times HR$ (487 ± 17)	Female QS2I = $QS2 + 1.7 \times HR$ (502 ± 15)
LVETI = $LVET + 1.1 \times HR$ (364 ± 10)	LVETI = $LVET + 1.2 \times HR$ (381 ± 16)
PEPI = $PEP + 0.5 \times HR$ (129 ± 10)	PEPI = $PEP + 0.5 \times HR$ (129 ± 10)
(PEP/LVET)I = 0.30 ± 0.04	(male and female)
Adolescents 13-19 years (Wandermann <i>et al.</i> , 1981):	
Male QS2I = $QS2 + 1.6 \times HR$ (498 ± 16)	Female QS2I = $QS2 + 1.7 \times HR$ (522 ± 14)
LVETI = $LVET + 1.0 \times HR$ (366 ± 11)	LVETI = $LVET + 1.3 \times HR$ (393 ± 10)
PEPI = $PEP + 0.5 \times HR$ (132 ± 13)	PEPI = $PEP + 0.4 \times HR$ (129 ± 11)
(PEP/LVET)I = 0.32 ± 0.05	(male and female)
Young adults 20-34 years (Burgess <i>et al.</i> , 1979; Warrington, personal communication):	
Male QS2I = $QS2 + 1.2 \times HR$ (506 ± 16)	Female QS2I = $QS2 + 1.6 \times HR$ (539 ± 15)
LVETI = $LVET + 1.1 \times HR$ (380 ± 11)	LVETI = $LVET + 1.6 \times HR$ (422 ± 11)
PEPI = PEP (116 ± 15)	PEPI = PEP (115 ± 11)
(PEP/LVET)I = $PEP/LVET - 0.002 \times HR$ (for female only)	
(PEP/LVET)I = 0.37 ± 0.05	(PEP/LVET)I = 0.23 ± 0.04
Weissler's regression equations 19-65 years:	
Male QS2I = $QS2 + 2.1 \times HR$ (546 ± 14)	Female QS2I = $QS2 + 2.0 \times HR$ (549 ± 14)
LVETI = $LVET + 1.7 \times HR$ (413 ± 10)	LVETI = $LVET + 1.6 \times HR$ (418 ± 11)
PEPI = $PEP + 0.4 \times HR$ (131 ± 10)	PEPI = $PEP + 0.4 \times HR$ (133 ± 10)
(PEP/LVET)I = 0.34 ± 0.04	(male and female)

with the normal standards established by Weissler for adults, QS2 and PEP were shorter in children at all heart rates and LVET was shorter at heart rate up to 85 beats per min in males and 105 beats per min in females (Cantor *et al.*, 1978). In adolescents, all STI are longer than those of children at all heart rates. When compared with adult values, PEP at all heart rates are shorter in adolescents while QS2 and LVET are shorter at the low or normal heart rates (Wanderman *et al.*, 1981). The PEP lengthens proportionally more than the LVET, resulting in a progressively higher PEP/LVET ratio with development, from childhood (0.30) to adolescent (0.32) to adulthood (0.34) (Wanderman *et al.*, 1981). In adults, a slight increase in PEP occurs with advancing age (Harrison *et al.*, 1964). The tendency of lengthening of STI seems to continue in the elderly who have longer LVET (Willems *et al.*, 1970) and QS2 (Slodki, Hussain and Luisada, 1969). No significant difference in STI between sexes was found in children (Golde and Burstin, 1970; Cantor *et al.*, 1978) and in adolescents (Wanderman *et al.*, 1981). In the adult, the differences in the regression equations for the sexes were significant for QS2 and LVET, but not for PEP (Weissler *et al.*, 1969).

Diurnal variation

A diurnal decrease in LVET and QS2 unaccompanied by a significant change in PEP occurs in normal subjects (Weissler *et al.*, 1965). This effect appears to reach its maximum between 4 pm and 8 pm and averages 8 and 10 msec for LVET and QS2 respec-

tively. It is for this reason that, as a standard procedure, the measurements should be made at the same time of the day preferably between 8 am and 10 am (Weissler *et al.*, 1972).

Day-to-day variation

It is important to appreciate the day-to-day variation in STI, both in normal subjects and in patients (Lewis *et al.*, 1977). This has been investigated by doing serial measurements of STI in both groups (Lewis, 1975). The mean one standard deviations of STI for individuals were smaller than the standard deviation values for the entire group. This indicates the consistency of STI, especially in normal subjects. The observed degree of day-to-day variation probably reflects variation in the degree of sympathetic drive to the heart (Johnson *et al.*, 1981). Burgess and associates (1979) found that variation in the measured STI due to the investigator, analyser, time and photocopying process is very small in comparison with the variability of the subjects being studied, with the possible exception of PEP where the analyser was responsible for about 14% of the observed variability.

Food

The STI should be performed in the post-absorptive state, as food intake has a positive inotropic effect (reduction in QS2I, PEP and PEP/LVET ratio) and chronotropic effect (Burgess, 1981). LVETI showed no significant change.

Pregnancy

Alterations in STI were found to occur during uncomplicated pregnancy (Rubler, Schneebaum and Hammer, 1973; Burg, Dodeck and Kloster, 1972; Kher, Grover and Durairaj, 1980). In the first and second trimesters, PEP was shortened and LVET prolonged, thereby significantly shortening PEP/LVET ratio. In the third trimester, the reverse was found, that is prolongation of PEP, reduction in LVET and an increase in PEP/LVET ratio. The findings in the first and second trimesters may suggest improved myocardial contractility. This improvement could be due to increased preload and ventricular diastolic filling resulting from the physiological increase in blood volume and also possibly due to hormonal influences. Decreased venous return and stroke volume by pressure of the gravid uterus on the inferior vena cava may be the explanation for the changes encountered in the third trimester in the supine position.

Validation of systolic time intervals

Validation of the STI has been a 2-stage process: first to establish the accuracy of external measurements, and second to correlate the STI with other, invasively obtained parameters of left ventricular function (Lewis *et al.*, 1977). Several investigations in man have established the validity of the STI as a true representation of the corresponding intervals, both in the steady state and during acute interventions. LVET derived externally from carotid arterial pulse tracing was compared with recordings obtained simultaneously from fluid-filled catheters in the proximal aorta (Weissler *et al.*, 1961; Robinson, 1963) and catheter-tip micromanometers in the central aorta (Bush *et al.*, 1970; Martin *et al.*, 1971; Van de Werf *et al.*, 1975). While external LVET is delayed in time, it was shown to be an accurate reflection of internally measured LVET and changes produced by acute interventions (Martin *et al.*, 1971) were identical when measured externally or internally. The external carotid arterial pulse tracing was almost identical to the intracarotid arterial pulse tracing (Van de Werf *et al.*, 1975). At resting heart rates, externally measured PEP was found to correlate closely with internally measured PEP (Bush *et al.*, 1970; Van de Werf *et al.*, 1975) and with true isovolumic contraction time (IVCT) (Martin *et al.*, 1971). Changes in PEP during acute interventions were identical to changes in true IVCT, thus validating the externally measured interval (Martin *et al.*, 1971). The narrow range of normal for QS2 at all heart rates and pressure supports its reliability as a useful measure of the duration of systole (Lewis *et al.*, 1977). The QS2 as measured externally ends with the first high frequency vibrations of the aortic compo-

nent of the second heart sound. The externally and internally recorded A2 corresponds exactly with the nadir of the central aorta pulse tracing incisura as studied by catheter-tip micromanometer (Bush *et al.*, 1970; Martin *et al.*, 1971). The delay between A2 to the nadir of the incisura of the external carotid arterial pulse tracing measures 10–35 msec at resting heart rates (Martin *et al.*, 1971; Van de Werf *et al.*, 1975).

In the second stage of the validation of the STI, correlations were performed between various STI and parameters of LV performance measured invasively. A good and significant correlation was found between PEP/LVET ratio and left ventricular ejection fraction determined angiographically among patients with a wide variety of cardiovascular diseases (Lewis *et al.*, 1976; Weissler, Stack and Sohn, 1980; Stack, Sohn and Weissler, 1981; Garrad, Weissler and Dodge, 1970; Ahmed *et al.*, 1972). In patients with coronary artery disease, the PEP/LVET ratio affords a highly reproducible measure of LV global performance that is equivalent in accuracy to the determination of LV ejection fraction (Stack *et al.*, 1981; Weissler *et al.*, 1980). Both PEP and LVET correlated significantly with the ejection fraction in patients with a wide variety of cardiovascular diseases (Garrad *et al.*, 1970). An inverse relationship between changes in left ventricular dp/dt and PEP was found in dogs (Metzger *et al.*, 1970) and in man (Martin *et al.*, 1971). In subjects with either normal LV or cardiac disease confined to the LV, PEP and PEP/LVET ratio exhibited excellent correlation with measures of contractility (contractile element velocity at peak dp/dt, and the Frank-Levinson contractility index) (Ahmed *et al.*, 1972).

Factors affecting systolic time intervals

The STI are dependent on four determinants; heart rate, preload, afterload, and myocardial inotropic state (Table 2).

PEP

Almost all authors agree that PEP is independent of heart rate. Increases in heart rate with atrial pacing or with vagal withdrawal by atropine do not change its value (Harris, Schoenfeld and Weissler, 1967). PEP varies inversely with stroke volume (Harley, Starmer and Greenfield, 1969; Weissler *et al.*, 1969). Reduction in preload and LV volume, as occur when normal persons assume an upright position (Stafford, Harris and Weissler, 1970), brisk diuresis (Weissler, 1977; Buch *et al.*, 1980), head-up tilt or application of venous occlusive tourniquets (Stafford *et al.*, 1970), results in prolongation of PEP. Reduction in end-diastolic volume may be associated with a reduction in the force of LV contraction, while reduction in end-diastolic pressure (LVEDP) is associated with an

TABLE 2. Factors affecting systolic time intervals

Interval	Increase	Decrease
PEP	– preload and SV + afterload, negative inotropic agents, impaired myocardial contractility	+ preload and SV – afterload, positive inotropic agents, enhanced myocardial contractility
LVET	+ preload and SV, + afterload, – afterload	– preload and SV, positive and negative inotropic agents
PEP/LVET	– preload, left ventricular diseases, negative inotropic agents,	+ preload, – afterload, positive inotropic agents,
QS2	negative inotropic agents	positive inotropic agents

Abbreviations: – reduction; + increase; SV stroke volume.

increase pressure gradient across the aortic valve. These factors lead to prolongation in PEP. On the other hand, increase in stroke volume due to enhanced ventricular filling is accompanied by an abbreviation in PEP (Greenfield *et al.*, 1968; Harley *et al.*, 1969; Weissler *et al.*, 1969). Changes in afterload are also important as aortic diastolic pressure determines aortic valve opening. Deviations in LVEDP may occur during pharmacological interventions. Reduction in peripheral resistance (Harris *et al.*, 1967; Sawayama *et al.*, 1969) results in shortening of PEP, while increase in peripheral resistance by angiotensin (Harris *et al.*, 1967) and methoxamine (Shaver *et al.*, 1968) prolongs PEP. PEP also depends on the myocardial contractility and inotropic state, so it is prolonged in heart failure (Weissler *et al.*, 1968) and myxoedema (Crowley *et al.*, 1977). Conversely, when LV contractility is increased as in thyrotoxicosis, PEP is short (Lien and Aandervd, 1982). PEP is shortened by positive inotropic agents and prolonged by negative inotropic agents (Harris *et al.*, 1967; Lewis *et al.*, 1976). Changes in the duration of the QRS complex and in the electromechanical interval will alter PEP, producing changes that have no haemodynamic significance (Metzger *et al.*, 1970).

LVET

This is related inversely to heart rate (Harris *et al.*, 1967; Weissler *et al.*, 1968). It reflects the duration that the aortic valve remains opened, thus it is directly related to stroke volume (SV) (Weissler, Harris and White, 1963; Weissler *et al.*, 1969; Harley *et al.*, 1969). LVET is reduced by decreased SV relative to end-diastolic volume as in heart failure and decreased preload (Lewis *et al.*, 1976), while enhanced left ventricular filling leads to prolongation of LVET. Both positive and negative inotropic agents cause a reduction in LVET (Lewis *et al.*, 1976), while

reduction and increase in afterload lead to prolongation of LVET. During methoxamine infusion, when SV, heart rate and inotropic state were held constant, LVET increased as mean arterial pressure increased (Shaver *et al.*, 1968). Decrease in afterload prolongs LVET (Sawayama *et al.*, 1969) due to the augmented stroke volume.

PEP/LVET ratio

This is relatively insensitive to changes in heart rate (Weissler *et al.*, 1968), although atrial pacing was found to increase it (Johnson *et al.*, 1981). It is increased with reduction in preload, negative inotropic agents and LV diseases (Weissler, 1977). Enhanced LV filling, positive inotropic agents and reduction in afterload lead to shortening of this ratio.

QS2

This is inversely related to heart rate and has been found to be variably affected by acute changes in SV brought about by changes in preload (Martin *et al.*, 1971). These findings support those of Harley *et al.*, (1969) who found the total duration of systole to increase when SV was augmented by an appropriate P-R interval during atrial pacing studies in patients with complete heart block. QS2 best reflects the presence of positive inotropic stimulation, since both PEP and LVET are shortened (Lewis *et al.*, 1976). A hallmark of the effect of positive inotropic agents is an abbreviation in QS2 and PEP (Weissler, 1977). A reduction in LVET usually, but not always, occurs, since associated haemodynamic changes such as an increase in stroke volume may have an opposite effect.

Use of systolic time intervals in clinical pharmacology

With the continuous flow of drugs into clinical

pharmacology, knowledge of their cardiovascular effects becomes mandatory. Here the contribution of STI as an investigative tool has become apparent. It is a non-invasive test which can be performed repeatedly and gives quantitative data about LV performance. It can reveal many important pharmacodynamic properties of the tested drug which may be of great therapeutic relevance, such as time of onset, duration of action, effect on chamber dynamics and the presence of possible chronotropic and inotropic actions. In the intact man, unlike the isolated heart, complex regulatory and intrinsic mechanisms act upon the heart and circulation. In pharmacological studies, where the drug can produce several haemodynamic influences, the study of the independent changes in heart rate, preload, afterload and myocardial contractility produced by the drug are often difficult. Because of these considerations, the STI should be viewed as a measure of chamber performance which, under the most rigorous condition, could be applied as a measure of contractility (Weissler *et al.*, 1980). The data provided by the STI when combined with other tests of ventricular function can yield a more comprehensive, and hence more valid analysis of ventricular performance.

The main clinical application of STI measurements today is in the study of the effects of drugs on the cardiovascular system (Table 3). Many drugs have been studied since the 1960's. Digitalis glycosides have been studied extensively in normal subjects and patients (Weissler *et al.*, 1964, 1965, 1970; Forester *et al.*, 1974; Burgess, Turner and Wadsworth, 1978; Matos, 1980). There was general agreement that they produce an abbreviation in QS2I, PEP and heart rate. The effect on LVET was more controversial, some investigators found consistent dose-dependent reductions (Weissler *et al.*, 1964), while others found no significant change. A temporal dissociation between chronotropic and inotropic actions of medigoxin was found in normal subjects (Burgess *et al.*, 1978).

Isoprenaline infusion into normal subjects produced positive chronotropic and inotropic actions with a dose-related abbreviation in PEP (Harris *et al.*, 1967). This reduction was due to the positive inotropic action of the drug and to the peripheral vasodilatation it produces. There was a concomitant shortening in LVET. Adrenaline and moderate doses of noradrenaline have similar actions (Harris *et al.*, 1967). Pharmacological vasoconstriction, both alpha-adrenergic (adrenaline and noradrenaline after propranolol) and by angiotensin, prolongs PEP (Harris *et al.*, 1967) and LVET. Atropine, 2 mg intravenously, abolished the vasoconstrictive-induced prolongation of PEP, although it augmented the pressor effect of noradrenaline and angiotensin. Atropine did not alter the PEP in normal subjects, nor did it inhibit

the prolongation due to other causes such as head-up tilt or the closing of systemic arterio-venous fistulae. Pharmacological vasoconstriction, therefore, appears to prolong PEP through reflex stimulation of the vagal efferent to the heart.

The effect of beta-adrenoceptor blockers on the duration of PEP varies with the specific agent used (Hunt *et al.*, 1970). The degree of change in PEP after intravenous propranolol was inversely proportional to its duration at rest (Ibrahim *et al.*, 1974). Individuals with increased sympathetic activity, including those with emotional tension and patients with phaeochromocytoma, show excessive lengthening of PEP in response to i.v. propranolol in comparison to a slight prolongation in normal subjects (Harris *et al.*, 1967). Propranolol produces a negative inotropic effect as indicated by prolonged PEP and PEP/LVET ratio, and a negative chronotropic effect in normal subjects and in patients with various cardiovascular diseases (Harris *et al.*, 1967; Hunt *et al.*, 1970; Ibrahim *et al.*, 1974; Frishman *et al.*, 1975; van Herick and Aronow, 1978), with no significant effect on LVETI. A negative inotropic action was found after oral oxprenolol in normal subjects (Frei, Imhof and Dubach, 1974) and in patients with coronary artery disease (Van Herick *et al.*, 1978). This was manifested as a significant prolongation of PEP and PEP/LVET ratio without an effect on LVETI and QS2I. Resting heart rate showed only a slight change (Van Herick and Aronow, 1978). Pindolol given i.v. to normal subjects produced no significant effect on any of the STI, which is probably because of its partial agonist activity (Weerasuriya, Warrington and Patel, 1981). However, when pindolol was given orally to patients with essential hypertension, it produced directionally opposite changes in STI. In those with normal pretreatment PEP/LVET ratios, it produced a significant increase in PEP and PEP/LVET ratio, and a significant decrease in LVETI, while those with abnormally high PEP/LVET ratios showed the opposite changes, i.e., a reduction in PEP and PEP/LVET ratio and a prolongation of LVETI (Plotnick *et al.*, 1980). This suggests that it has different mechanisms for changing cardiac function in the 2 groups.

Beta-blockade effect predominates in the first group while the intrinsic sympathomimetic effect of pindolol counteracts the beta-blocking effect in the second group. In both situations, no significant change in heart rate was found.

In normal subjects, amyl nitrate inhalation produced a significant prolongation in LVETI and a significant reduction in PEPI, while patients with ischaemic heart disease exhibited no significant changes, probably due to lack of increase in stroke volume and/or in contractility of the ischaemic myocardium (Sawayama *et al.*, 1969). Glyceryl

TABLE 3. Effects of some drugs on systolic time intervals

Drug	Significant STI changes	Possible mechanisms
Digitalis glycosides	– PEP and QS2I	positive inotropic effect
Catecholamines	– PEP and QS2I	positive inotropic effect
Propranolol	+ PEP and PEP/LVET	negative inotropic effect
Oxprenolol	+ PEP and PEP/LVET	negative inotropic effect
Pindolol (a) hypertensives with high PEP/LVET.	none in normal subjects – PEP and PEP/LVET + LVETI	partial agonist partial agonist
(b) hypertensives with normal PEP/LVET	+ PEP and PEP/LVET – LVETI	negative inotropic effect
GTN	– QS2I and LVETI	reflex inotropic
Amyl nitrate	– PEP + LVETI	afterload reduction
Hydralazine	– PEP	positive inotropic effect
Calcium gluconate	– QS2I and LVETI	positive inotropic effect
Prostacyclin	– PEP and QS2I + LVETI	reflex inotropic increased SV
PGF2-alpha	– PEP and PEP/LVET	positive inotropic effect
PGE2	– PEP and PEP/LVET	afterload reduction

Abbreviations: – decrease; + increase.

trinitrate (GTN), when given sublingually to normal subjects, produced an increase in heart rate, a decrease in QS2I and LVETI and little alteration in PEP and PEP/LVET ratio (Warrington and Burgess, 1980). These results are compatible with a vasodilator action of GTN, predominantly on the venous circulation with consequent mild tachycardia and inotropic stimulation. Oral hydralazine elicits a positive inotropic action in patients with left ventricular failure, shown as a significant shortening of PEP and an increase in the mean rate of rise of isovolumic pressure (Leier *et al.*, 1980). The effect of prazosin on these inotropic variables was negligible. Amitriptyline increased the PEPI and PEP/LVET ratio, while mianserin has no effect on STI (Burgess *et al.*, 1978). The finding with amitriptyline may indicate a decrease in myocardial contractility. The effect of acute changes in serum calcium upon STI may reflect an inotropic action of this ion on the human heart (Shiner *et al.*, 1969), as infusion of 10% calcium gluconate consistently shortened QS2 and LVET and slowed heart rate.

The effect of various prostaglandins on STI have also been studied. Prostacyclin infusion produced a dose-related decrease in diastolic blood pressure, PEP and QS2I (Warrington, Smith and O'Grady, 1980) and an increase in LVETI (Hassan *et al.*, 1982).

Pretreatment of the subjects with atenolol or propranolol did not modify these STI findings. Infusion of prostaglandin F2 alpha (PGF2 alpha) in 5 healthy pregnant women during abortion produced a significant rise in cardiac output, arterial blood pressure and a significant reduction in PEP and PEP/LVET ratio. This suggests that it may have a positive inotropic action, as rising cardiac output and blood pressure should increase the PEP (Thayssen, Secher and Arnsbo, 1981). On the other hand, PGE2 infused into another 5 women under the same conditions produced a significant fall in PEP and PEP/LVET ratio consequent to the fall in peripheral resistance which occurred (Thayssen *et al.*, 1981). No significant rise in LVETI was seen in either situation.

Another application for the use of STI is in patients receiving adriamycin for treatment of malignant diseases; here, monitoring of PEP/LVET ratio may detect early cardiotoxicity and prevent life-threatening heart failure (Rinehart, Lewis and Bolcerzak 1974; Al-Ismael and Whittaker, 1979).

The study of systolic time intervals in diseases

The application of STI in clinical practice is based on the fact that they are well regulated under normal circumstances so that they fall within narrow physio-

TABLE 4. Effects of some diseases on systolic time intervals

Disease	Possible Systolic Time Interval Changes
Chronic myocardial dysfunction	long PEP, short LVETI, high PEP/LVET and normal QS2I
Acute myocardial infarction	early: short PEP, LVETI and QS2I, late: long PEP and short LVETI
Aortic stenosis	short PEP, long LVETI, low PEP/LVET and long QS2I
Aortic regurgitation	short PEP, long LVETI and low PEP/LVET
Mitral stenosis	short LVETI
Mitral regurgitation	usually normal STI
Left bundle branch block	long PEP and high PEP/LVET
Hypothyroidism	long PEP, short LVETI and high PEP/LVET
Hyperthyroidism	short PEP, long LVETI and low PEP/LVET
Diabetes mellitus	long PEP, short LVETI and high PEP/LVET
Chronic alcoholism	long PEP, short LVETI and high PEP/LVET

logical limits (Weissler, 1977), and that alterations in STI reflect not only transient haemodynamic changes but also accompany sustained alterations in LV performance. It is on these facts that the interest in the study of STI changes in various cardiovascular diseases (Table 4) is based (Weissler *et al.*, 1972). In chronic myocardial diseases (Weissler *et al.*, 1968; 1969), the typical STI pattern of left ventricular dysfunction is prolongation of PEP, shortening of LVETI, and normal QS2I. Among patients with reduced cardiac output (CO), the magnitude of deviation in PEPI and LVETI correlates closely and significantly with stroke volume (SV) and cardiac output (Weissler *et al.*, 1972), the more severe the disease, the more marked the deviations. Furthermore, among patients in whom CO and SV fell within normal limits, significant deviations in PEPI and LVETI were still frequent. Thus, while the changes in STI might accompany alteration in SV and CO, they probably were not causally related to these haemodynamic events. Rather it appeared that the changes in STI were the direct result of overall changes in LV performance (Weissler *et al.*, 1972). A good correlation between PEP/LVET ratio and stroke index was found among patients with arteriosclerotic, hypertensive, and primary myocardial diseases (Weissler *et al.*, 1969). The PEP/LVET ratio was found to be a more sensitive index of left ventricular dysfunction than is the cardiac index or stroke index (Lewis *et al.*, 1970). Increased PEP/LVET ratio to 0.44 or greater may denote the presence of diminished LV performance, mild (0.44–0.52), moderate (0.53–0.60) and severe more than 0.60 (Weissler, 1977). Patients with hypertension and minimal functional impairment may show no

abnormalities in STI (Weissler *et al.*, 1969; Ibrahim *et al.*, 1974; Plotnick *et al.*, 1980). In the course of acute myocardial infarction (AMI), an early observation was shortened QS2I in nearly all patients (Toutouzas *et al.*, 1969). Subsequently, this was found to be due to high adrenergic tone in AMI (Lewis *et al.*, 1972), and a strong correlation was found between urinary adrenaline and noradrenaline excretion and QS2I. This shortening of QS2I can be reversed towards normal by administration of IV propranolol (Lewis *et al.*, 1976). The high adrenergic tone will profoundly affect the usual pattern of prolongation of PEP and shortening seen in the presence of myocardial dysfunction (Lewis *et al.*, 1976). Thus, a normal PEPI and PEP/LVET ratio in AMI with the high level of adrenergic tone actually represents LV dysfunction (Lewis *et al.*, 1977). Among patients who convalesce after previous AMI, the STI may reveal the presence of residual abnormalities, e.g. an increase in PEPI and PEP/LVET ratio when clinical and radiological evidence for such cardiac abnormality is absent (Weissler *et al.*, 1980). Favourable survival rate among patients with a previous MI is when their PEP/LVET ratio is normal even in the presence of two or three vessel disease, while those with abnormal ratio have diminished survival (Weissler *et al.*, 1981). In coronary artery disease, the PEP/LVET ratio was found to correlate with the angiographically determined left ventricular ejection fraction (Lewis *et al.*, 1976) and to have a significant prognostic value (Gillilan *et al.*, 1979). On life-table analysis, the difference between subjects with resting PEP/LVET ratio more than 0.50 and those with a ratio less than 0.50 was highly significant. The ratio was more predictive of mortality than other para-

TABLE 5. Non-invasive techniques to study cardiac function and performance

Method	Cost	Convenience to patients	Ease of learning	Application to all subjects
Systolic time intervals	cheap	convenient	easy	almost all
Apex cardiography	cheap	convenient	easy	almost all
Ultrasound study				
M-mode echo	expensive	convenient	difficult	not all
Two-dimensional	expensive	convenient	difficult	not all
Radionuclide imaging techniques	expensive	less convenient	difficult	not all
Impedance plethysmography	expensive	convenient	difficult	almost all
Cardiac output measurement using indocyanine green dye solution	cheap	convenient	easy	almost all

meters including resting ECG, maximum tolerance testing data and cardiac catheterization. However, others (Parker and Just, 1974) doubted the value of STI in the clinical assessment of coronary artery disease. They found no group deviation from normal and no significant correlation between either STI absolute values or their changes with dp/dt max, ejection fraction, or asynergy was found. In anaemia, uraemia, nephrotic syndrome and liver cirrhosis where fluid overload may cause pulmonary oedema, STI are usually normal, if no underlying heart disease is present (Lewis, 1975). Prolongation of PEPI and PEP/LVET ratio with shortening of LVETI indicating cardiac depression may be found in diabetes mellitus (Ahmed *et al.*, 1975), hypothyroidism (Crowley *et al.*, 1977) and in chronic alcoholism (Spodick *et al.*, 1972). In diabetes mellitus, the STI changes were independent of duration and mode of therapy of the disease.

Systolic time intervals and decision making

A recently applied clinical use of STI is in the study of the cardiovascular system before, during and after operations (Dauchat and Gravenstein, 1980). Pre-operatively, the STI can offer information regarding cardiac performance, although normal STI do not exclude the presence of heart disease. Intra-operatively, automated STI monitoring provide continuous data acquisition and instantaneous delivery of information about haemodynamic changes, effects of drugs and anaesthetics used on the cardiovascular system, and responses to treatment (calcium, fluid replacement, afterload reduction). Postoperatively, STI may be helpful prognostically and in assessment of the results of medical and surgical treatment as in coronary artery disease (Lewis *et al.*, 1976).

Place of systolic time intervals among other non-invasive techniques

Several non-invasive techniques (Table 5) have been developed to assess myocardial function and performance, and it is necessary to put systolic time intervals in perspective among them. In evaluating their use in clinical practice, several considerations must be remembered (Shine *et al.*, 1980):

(1) Can the procedure produce results that will spare the patient additional investigations of greater risk, discomfort or cost?

(2) Does the procedure represent a new quantitative standard for diagnosis or treatment that may potentially replace currently available procedures at a lower morbidity or cost?

(3) Will the procedure permit repetitive evaluation of a patient for study of the natural history of disease, response to therapy or the outcome of interventions?

The three principal methods in use at present include systolic time intervals, M-mode and cross-sectional echocardiography and radionuclide angiography (Braunwald, 1980). Some of these procedures need increasingly sophisticated and expensive equipment ranging from the electronic scanners for echocardiographic use to radionuclide techniques requiring a cyclotron (Shine *et al.*, 1980). Echocardiography and radionuclide angiography provide alternative methods to contrast angiography for measurements of ventricular volume and/or dimensions, and allow the non-invasive estimation of ejection phase indices (Braunwald, 1980). Echocardiography is an accepted non-invasive tool for the assessment of cardiac anatomy and function. Nevertheless, it has important limitations including high cost, the need to understand unfamiliar tomographic anatomy, a variable image presentation making standardization difficult and a need for greater physician-technician

interaction for the best results (Seward and Tajik, 1980). The M-mode echo assesses only a small portion of the ventricular myocardium and does not always represent the overall left ventricular performance. Despite improvements in echo techniques and instrumentation, there are still many patients in whom it is difficult to record satisfactory echocardiograms and this represents a significant limitation of its use (Feigenbaum, 1980). Whether the heart is examined with an M-mode or cross-sectional device, proper angulation of the ultrasonic beam is critical. Echo controls can also influence the image profoundly and the operator must be skilled to ensure that artifacts and distortion are not introduced through improper use of the gain control. Thus, although the echo examination is simple and painless for the patient, it can be extremely difficult to perform, so that a well trained individual is required for both the examination and the interpretation of results (Feigenbaum, 1980). Radionuclide imaging of the heart and cardiovascular system have important implications for the functional evaluation of patients with cardiac disorders, especially those with coronary artery disease (Maisey, Hilson and Wainwright, 1982). The two techniques which have the widest application at present are rest-and-stress thallium-imaging of the myocardium, and radionuclide ventriculography (Maisey, *et al.*, 1982). However, the use of radionuclide imaging of the heart to study drug effects is limited.

In clinico-pharmacological assessment of myocardial performance, measurement of systolic time intervals has some favourable advantages over other non-invasive techniques. It is a quantitative measurement that requires relatively cheap equipment and can be carried out in almost all subjects without discomfort. The technique can be easily learnt, and within- and between-observer accuracy is good (Burgess *et al.*, 1979). However, in the assessment of positive inotropic effect of drugs, STI and M-mode echo are complementary and both are less sensitive than dp/dt max measured during cardiac catheterization (Walsh, Crawford and O'Rourke, 1982).

Conclusions

The STI is a helpful, non-invasive method to study left ventricular performance in health and disease. One must remember that it is virtually impossible to interpret STI findings without knowledge of the clinical setting in which the measurements are made and the physiological and pharmacological influences which affect performance of the heart (Weissler, 1980). The complex regulatory and intrinsic mechanisms controlling the heart and circulation in intact subjects make it difficult to draw definitive final conclusions from STI especially in pharmacological studies. Tests of ventricular contractility are,

therefore, best confined to controlled studies on single ventricle or isolated cardiac muscle preparations. The STI, finally, should be viewed as a measure of chamber performance which is not competitive with other invasive or non-invasive tests of cardiac function, but is particularly well suited to clinical pharmacological studies.

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